PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 08 MAR 2006
WIPO PCT

Applicant's or agent's file reference JW01080WO	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/GB2004/004996	International filing date *(day/month/year)* 29.11.2004	Priority date *(day/month/year)* 28.11.2003
International Patent Classification (IPC) or national classification and IPC A61K35/76		
Applicant QUADRANT DRUG DELIVERY LIMITED et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.06.2005	07.03.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Marinoni, J-C Telephone No. +49 89 2399-8563

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004996

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-13 as originally filed

Claims, Numbers

1-28 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/004996

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

   see separate sheet

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-28
	No:	Claims	none
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-28
Industrial applicability (IA)	Yes:	Claims	1-28
	No:	Claims	none

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Re Item II

Priority

The priority appears to be validly claimed.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Introduction

The present application relates to a method for producing a micro-particle dry powder comprising a viral particle, said method comprising the step of spray-drying a mixture of the viral particle and a stabilising carbohydrate using an outlet temperature of no more than 60°C.

2. Documents cited

D1: WO 00/00215, 6 January 2000
D2: WO 02/32398, 25 April 2002
D3: WO99/555362, 4 November 1999
D4: WO02/066005, 29 August 2002
D5: WO 96/03978, 15 February 1996

3. Novelty

None of the available documents discloses such a method. The subject-matter of **claims 1-28** therefore meets the requirements of Art. 33(2) PCT concerning novelty.

4. Inventive step

4.1. Applicant's arguments concerning inventive step have been carefully considered. However, the objections of lack of inventive step are maintained.

4.2. Document **D1** is considered as the closest prior art. **D1** discloses (example XIV) a method for producing a microparticle dry powder for pulmonary administration comprising a live influenza virus (a complex envelopped virus) and a carbohydrate (hydroxyethyl starch) at outlet temperatures of 61°C, and comprising the use of a non-aqueous compound as perfluorocarbon. **D1** also shows protection against challenge of mice immunized with said influenzy-containing micro-particles through

administration via nasal route.
D1 further provides a list of some live attenuated or killed viruses that could be used in said method. Said list comprises measles.
D1 further provides a list of some carbohydrates that could be used alternatively. Said list includes "monosaccharides such as dextrose (anhydrous and monohydrate), galactose, mannitol, D-mannose, sorbitol, sorbose and the like; disaccharides such as lactose, maltose, sucrose, trehalose, and the like; trisaccharides such as raffinose and the like".
D1 further provides a list of non-aqueous compounds that could be used in said method. Apart from perfluorocarbons, said list includes oils in general, and glycerol and glycol derivatives.
D1 further describes that, in connection with the production of powders for lung deposition, "exemplary settings are as follows: an air inlet temperature between 60°C and 170°C; an air outlet between 40°C to 120°C".

4.3. Applicant contends that the present invention overcomes the problem of the low yield (1%) of live virus recovery obtained with the method of **D1.** However, the examples on file do not address this problem and do not provide numerical values for live virus recovery in connection with low temperature. On page 11, l. 32-33, the applicant states that "using a low trehalose feed concentration with both high and low outlet temperatures, virus losses are considerable" and on page 12, l. 2-4 "an increase in trehalose concentration is responsible for a rise in virus recoveries". The examples therefore rather indicate that some correct combinations of trehalose concentration and outlet temperature conditions are necessary to carry out the invention in order to solve the technical problem. Furthermore, without comparative examples, it cannot be believed that a difference of 1°C in outlet temperature will have an incidence on the yield of live virus so as to make the claimed method inventive.
Therefore in accordance with the technical problem identified by the applicant and fully agreed upon by the IPEA ("a method for the improved retention of activity of virus particle on spray-drying"), and in view of the results presented in the application, the solution cannot be seen as residing solely in the provision of a method wherein the outlet temperature is below 60°C.

4.4. Additionally, concerning the outlet temperature (which appears to be the most

important feature in the method as presently claimed), it is considered that the prior art already discloses methods wherein dry powder compositions possibly comprising virus particles combined to a carbohydrate could be obtained at temperatures below 60°C and sometimes at room temperature (see *e.g.* **D5** (and not **D4** as accurately mentioned by the Applicant) which was cited in the ISR and which discloses spray-dried live attenuated virus composition comprising trehalose, at inlet temperature of 40°C).

4.5. It is also noted that the prior art often mentions inlet temperatures but not outlet temperatures. However, it appears that outlet temperatures are generally lower than inlet temperatures and that therefore the outlet temperatures in said prior art documents must be below 60°C (see also tables 1 and 2 of the present application). The prior art also identifies that to obtain such powders comprising peptidic antigens for use as vaccines or other compounds temperatures below 60°C or in overlapping ranges are advantageous (see **D2**, 50-55°C; **D3**, "30 to 50°C, with 40°C being preferred").

4.6. The subject-matter of **claims 1-21,23-28** does therefore not meet the requirements of Art. 33(3) PCT concerning inventive step.

4.7. Document **D2** discloses the spray drying of virus including measles and a carbohydrate ("monosaccharides (*e.g.*, dextrose, fructose, inositol), disaccharides (*e.g.*, sucrose, saccharose, maltose, lactose), or polysaccharides (*e.g.*, cellulose, glycogen, starch)") and possibly a non-aqueous component (including glycerol an glycol derivatives, soybean (*i.e.* soya) oil, peanut (*i.e.* arachis) oil or sesame oil). The provision of a method where the non-aqueous component is an oil as defined in **claim 22** does therefore not meet the requirements of Art. 33(3) PCT concerning inventive step.

4.8. All other combinations, including concentration of carbohydrate, spray-dryer nozzle-tip configuration, appear to merely depend upon the carbohydrate/non-aquous component combination chosen and are considered to be easily obtained through experimention by the skilled person according to the circumstances.

4.9. It is however possible that a particular combination of features (*e.g.* a particular type of virus, a particular range of temperature, a particular carbohydrate and a particular non-aqueous compound), said combination being disclosed and exemplified in the application as filed, may involve an inventive step.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
GB2395900	09.06.2004	04.12.2002	